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REMARKS

The present application was originally filed with 17 Claims. In response to a Restriction Requirement dated April 23, 2003, Applicants elected the Claims in Group I (Claims 1-6 and 8-16), cancelled Claims 7 and 17, and elected enzymes as the species (*i.e.*, as recited in Claims 6 and 16). As indicated in the Response filed July 16, 2003, Applicants request that the remaining species be examined, upon the determination that the enzyme species are patentable. In the present Response, Applicants have cancelled Claims 1-6, without prejudice. Applicants reserve the right to pursue these, similar, and/or broader Claims in other application(s).

Applicants note that the priority filing date has been acknowledged. The Examiner has indicated that two publications cited in the Information Disclosure Statement are not in compliance, due to missing publication dates. Applicants respectfully submit that no publication dates are available for these two publications (the Quikchange and Benchmark references). Thus, Applicant cannot provide the missing information. Applicants thank the Examiner for catching the typographical error in the paragraph beginning at page 2, line 26, of the present Specification. Applicants have corrected the error in the present amendments. No new matter is added to the Specification by this or any of the other amendments. The Examiner's rejections are addressed below in the following order:

- 1) Claims 1-6 and 8-16 stand rejected under 35 USC §112, second paragraph;
- 2) Claims 1-6, 8, and 11-16 stand rejected under 35 USC §102(b);
- 3) Claims 1-6, 8, and 11-16 stand rejected under 35 USC §103(a);
- 4) Claims 1-6 and 8-16 stand rejected under 35 USC §101; and Claims 1-6 and 8-16 stand rejected for alleged non-statutory double patenting.

1) The Claims are Definite

The Examiner has rejected Claims 1-6 and 8-16 under 35 USC §112, second paragraph, as allegedly being indefinite. In particular, the Examiner points to various recitations within the Claims. As Applicants have cancelled Claims 1-6, the rejection is moot as to these Claims. In regard to Claims 8-16, Applicants have amended the Claims to provide a more clear recitation.

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In regards to Claim 16, Applicants respectfully submit that no amendment to the "said protein product" recitation is needed. Claim 16 depends from Claim 15, which recites "... protein product." Thus, there is sufficient antecedent basis for the recitation of "said protein product" in Claim 16. As the amended Claims are clearly definite, Applicants respectfully request that this rejection be withdrawn.

2) The Claims are Novel

The Examiner has rejected Claims 1-6 8, and 11-16 under 35 USC §102(b). In particular, the Examiner indicates that the Claims are allegedly anticipated by U.S. Patent No. 5,932,419 to Bauer *et al.* In regards to Claims 1, 8 and 12, the Examiner argues that the Bauer *et al.* Patent discloses a method for introducing site-directed mutations into circular DNA molecules of interest by means of mutagenic primer pairs, which anticipates Claim 1. However, there are no arguments as to the anticipation of Claims 8 or 12 in the present Office Action. Nonetheless, Applicants must respectfully traverse the Examiner's rejection and submit that present Claims are novel over the Bauer *et al.* Patent. As repeatedly indicated by the Courts, "[A]nticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention."²

Unlike the presently claimed invention, the Bauer *et al.* reference teaches the use of one primer pair, in which the primers are complementary (at least partially) to each other. Furthermore, these primers are both mutagenic primers (*See e.g.*, col. 6, lines 46-48; col. 6, lines 57-59; col. 7, lines 5-9; Claim 1, etc.).

In contrast, the presently claimed invention does not require the use of mutagenic primer pairs. Rather, as in amended Claim 8, only one of the primers used is mutagenic. In new Claim 19, at least three primers are used in the method, at least one of which is mutagenic. As these embodiments are not taught, nor mentioned in the Bauer *et al.*, Patent, these Claims are novel over the Bauer *et al.* Patent. These amendments find more than sufficient support in the Specification as filed (*See e.g.*, the Summary and Examples). Applicants respectfully submit that because the dependent Claims incorporate all of the elements of the independent Claims, the dependent Claims are likewise not anticipated by the Bauer *et al.* Patent. As the Bauer *et al.*

²RCA Corp. v. applied Digital Data Sys., Inc., 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984).

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Patent does not disclose each and every element of the presently claimed invention, Applicants respectfully request that this rejection be withdrawn.

3) The Claims are Unobvious

The Examiner has rejected Claims 1-6, 8, and 11-16 under 35 USC §103(a), under the Bauer *et al.* Patent (*See, above*), and Stemmer *et al.* (U.S. Patent No. 5,512,463) (Stemmer *et al.* Patent). In particular, the Examiner indicates that for Claims 1-6, 8, and 11-16, the Bauer *et al.* Patent teaches all of the claimed elements. Applicants must respectfully disagree. Furthermore, Applicants note that the Examiner admits that the Bauer *et al.* Patent does not teach the use of 3-15 primers (*e.g.*, Claims 9 and 20 of the presently claimed invention); and that the Bauer *et al.* Patent does not teach the use of discontiguous primers (*e.g.*, Claims 10 and 21 of the presently claimed invention).

The Examiner argues that the Stemmer *et al.* Patent teaches methods for producing nucleic acid libraries by preparing first and second primer populations that hybridize to a double-stranded nucleic acid template that is subsequently amplified. However, the Examiner admits that the Stemmer *et al.* Patent only teaches exponential amplification (*e.g.*, PCR). Therefore, the Stemmer *et al.* Patent does not teach the use of linear amplification, as in the presently claimed invention.

The Examiner further argues that the Stemmer *et al.* Patent teaches the use of four primers and the general teaching of the Patent would allow one of skill in the art to “. . . immediately envision any number of primers. . .” [Office Action, page 10]). The Examiner also argues that the Stemmer *et al.* Patent teaches that the primers are discontiguous.

In sum, the Examiner argues that it would have been obvious to one skilled in the art to replace the exponential amplification of the Stemmer *et al.* Patent for production of combinatorial nucleic acid libraries with the linear amplification method of the Bauer *et al.* Patent, because the Bauer *et al.* Patent explicitly states the linear amplification is better than exponential amplification. Thus, the Examiner argues that one of skill in the art would have been motivated to use the linear amplification in order to reduce the time and expense of generating hosts and transforming hosts with other methods for site-directed mutagenesis. The

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Examiner also argues that one of skill in the art would reasonably have expected to be successful because the Stemmer *et al.* Patent teaches that both “overlapping” and “non-overlapping” primers can be used, which would encompass the “overlapping primers” or “partially overlapping” primers disclosed in the Bauer *et al.* Patent. Applicants must respectfully disagree with the Examiner’s arguments and traverse this rejection.

Applicants respectfully submit that as indicated above, there is nothing in the Bauer *et al.* Patent that teaches or even remotely suggests the presently claimed invention. Furthermore, the teachings of the Stemmer *et al.* Patent do not fill in the gaps in this teaching, such that the present Claims are even suggested. Although Stemmer *et al.* teaches the use of “primer populations” (*See*, col. 17, lines 19-31) that can include primers that overlap on the template, are contiguous or discontiguous, Stemmer *et al.* fail to teach a method in which at least two primers are used, wherein one primer is in opposite orientation to the remaining primers and at least one primer is a mutagenic primer that corresponds to a desired mutation. The definition of “primer population” in Stemmer *et al.* (*See*, col. 17, lines 19-31) indicates that the term “is used to describe the pool of primers that have identical base compositions except at certain predetermined locations along the sequence that contain a variable composition.” In contrast, the presently claimed invention does not rely on the use of “primer populations.” Rather, the primers used in the presently claimed invention are designed such that at least two primers are mixed, one of which is a mutagenic primer and at least one is in opposite orientation to the remaining primers. In the Stemmer *et al.* Patent, the two primer populations are oriented in opposite directions. Thus, there is no teaching in the Stemmer *et al.* Patent of the primers used in the methods presently claimed. As the Bauer *et al.* and Stemmer *et al.* Patents fail to teach or suggest the presently claimed invention, Applicants respectfully submit that the presently claimed invention is unobvious over these Patents. Thus, Applicants respectfully request that this rejection be withdrawn.

4) There is No Double-Patenting

The Examiner has rejected Claims 1-6 under 35 U.S.C. §101, as claiming the same invention of Claims 1-6 of co-pending U.S. Pat. Appln. Ser. No. 09/729,520. In addition, the Examiner has rejected Claims 1-6 and 8-16 for alleged obviousness-type double patenting as

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being provisionally unpatentable over Claims 1-6 of co-pending U.S. Pat. Appln. Ser. No. 09/729,520, in view of the Bauer *et al.* and Stemmer *et al.* Patents.

Applicants respectfully submit that there is no double patenting. Claims 1-6 have been cancelled in the present amendments. Furthermore, upon receiving notification of allowance of the Claims, Applicants will provide a terminal disclaimer to remove the obviousness-type double patenting rejection.

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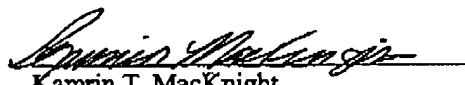
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CONCLUSION

All grounds of rejection and objection of the Office Action of September 4, 2003, having been addressed, reconsideration of the Claims is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned at (650) 846-5838.

Respectfully submitted,

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